Boron-Containing Heterocycles: Syntheses, Structures, and Properties of Benzoborauracils and a Benzoborauracil Nucleoside

Jin-Cong Zhuo,*,† Albert H. Soloway,† John C. Beeson,‡ Weihua Ji,† Beverly A. Barnum,† Feng-Guang Rong,† Werner Tjarks,† Glenn T. Jordan IV,§ Jianping Liu,§ and Sheldon G. Shore§

College of Pharmacy and the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received July 23, 1999

Benzo-fused boron-containing heterocycles (benzoborauracils**),** 1-hydroxy-1*H*-2,4,1-benzodiazaborin-3-one (**3a**), 1-hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (**3b**), and 1-hydroxy-2-phenyl-1*H*-2,4,1-benzodiazaborin-3-one (**3c**) were synthesized, and their structures were established on the basis of ^{1}H, ^{13}C, and ^{11}B NMR spectroscopies, mass spectrometry, and microelemental analyses. The structures of compounds **3b** and **3c** were unambiguously confirmed by X-ray crystallographic analyses. ^{11}B NMR spectral analyses of the methanolic solutions of benzoborauracils **3a**−**c** confirmed the formation of the corresponding bis-methanol adducts **13a**−**c**. The structure of the *N*-Ph bis-methanol adduct **13c** was confirmed by X-ray crystallography. The stabilities of these bis-methanol adducts depend on the substituent at the N2 position of **3a**−**c**. The bis-methanol adducts are readily reconverted to the corresponding benzoborauracils upon removal of methanol. The first stable benzoborauracil nucleoside, 4-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-disopropylidene-α-D-ribofuranosyl]-1-hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (**25**) was prepared in two steps by treatment of 2-aminophenylboronic acid with 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-diisopropylidene-D-ribofuranose followed by its reaction with methylisocyanate.

Introduction

The chemistry of boron neutron capture therapy (BNCT) has been summarized in a recent review.[1] This potential use of boron compounds for the treatment of cancer is based upon the unique nuclear properties of the nonradioactive ^{10}B nucleus and its propensity to absorb thermal neutrons. The resulting activated ^{11}B nucleus, following this capture reaction, undergoes prompt fission. The size and energy of the particles emitted are very large by nuclear standards and provide the basis for attempting to destroy malignant cells selectively without adversely affecting surrounding or nearby normal cells. In essence, this is a binary chemoradiotherapeutic procedure that is totally dependent upon the specific targeting of tumor cells by boron compounds.

The boron-containing delivery agent should be nontoxic, selectively target tumor cells, and ideally localize within the nucleus. Various boron-containing analogues of biologically active compounds, such as amino acids,[2] peptides,[3] porphyrins,[4] polyamines,[5] as well as DNA binders,[6] have been synthesized and considered as potential agents for BNCT. If they function in a manner similar to their naturally occurring counterparts and become selectively incorporated into either proliferating or metabolically active tumor cells, then they may have potential as BNCT agents.

Boron-containing nucleosides[7] are potentially attractive compounds because they may be (1) taken up selectively into tumors due to the high mitotic rate of tumor cells vs normal cells, (2) intracellularly converted to the corresponding nucleotides through phosphorylation by appropriate enzymes such as TK1 or dCK, and (3) potentially incorporated into tumor DNA, thereby enhancing the cytotoxity of the neutron capture reaction. Early work focused on the development and synthesis of boron-containing purine and pyrimidine bases in which the boron atom was placed within the purine or pyrimi-

† College of Pharmacy.
‡ Deceased.
§ Department of Chemistry.

(1) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.

(2) (a) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7529−7530. (b) Malan, C. Morin C. *J. Org. Chem.* **1998**, *63*, 8019−8020. (c) Takagaki, M.; Ono, J.; Oda, Y.; Kikuchi, H.; Nemoto, H.; Iwamoto, S.; Cai, J.; Yamamoto, Y. *Cancer Res.* **1996**, *56*, 2017−2020. (d) Wyzlic, I. M.; Tjarks, W.; Soloway, A. H.; Perkins, D. J.; Burgos, M.; O'Reilly, K. P. *Inorg. Chem.* **1996**, *35*, 4541−4547. (e) Nemoto, H.; Cai, J.; Asao, N.; Iwamoto, S.; Yamamoto, Y. *J. Med. Chem.* **1995**, *38*, 1673−1678. (f) Radel, P. A.; Kahl S. B. *J. Org. Chem.* **1996**, *61*, 4582−4588. (g) Karnbrock, W.; Musiol, H. J; Moroder, L. *Tetrahedron* **1995**, *51*, 1187−1196.

(3) (a) Leush, A.; Jungblut, L.; Moroder, L. *Synthesis* **1994**, 305. (b) Kane, R. R.; Pak, R. H.; Hawthorne, M. F. *J. Org. Chem.* **1993**, *58*, 8. 991−992. (c) Kane, R. R.; Hawthorne, M. F. *Bioconjugate Chem.* **1991**, *2*, 242−253. (d) Schwyzer, R.; Do, K. Q.; Eberle, A. N.; Fauchère, J. L. *Helv. Chim. Acta* **1981**, *24*, 1409.

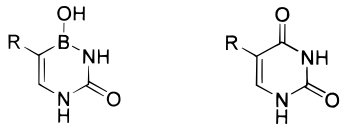
(4) (a) Miura, M.; Micca, P. L.; Fisher, C. D.; Gordon, C. R.; Heinrichs, J. C.; Slatkin, D. N. *Br. J. Radiol.* **1998**, *71*, 773−781. (b) Phadke, A. S.; Morgan, A. R. *Tetrahedron Lett.* **1993**, *34*, 1725−1728. (c) Miura, M.; Gabel, D.; Oenbrink, G.; Fairchild R. G. *Tetrahedron lett.* **1990**, *31*, 2247−2250. (d) Kahl S. B.; Koo M.-S. *J. Chem. Soc., Chem. Commun.* **1990**, 1769−1771.

(5) (a) Cai, J.; Soloway, A. H.; Barth, R. F.; Adams, D. M.; Hariharan, J. R.; Wyzlic, I. M.; Radcliffe, K. *J. Med. Chem.* **1997**, *40*, 3887−3896. (b) Cai, J.; Soloway, A. H. *Tetrahedron Lett.* **1996**, 9283−9286.

(6) (a) Yamamoto, Y.; Cai, J.; Nakamura, H.; Sadayori, N.; Asao, N.; Nemoto, H. *J. Org. Chem.* **1995**, *60*, 3352−3357. (b) Kelly, D. P.; Bateman, S. A.; Hook, R. J.; Martin, R. F.; Reum, M. E.; Rose, M.; Whittaker, A. R. D. *Aust. J. Chem.* **1994**, *47*, 1751−1769. (c) Kelly, D. P.; Bateman, S. A.; Martin, R. F.; Reum, M. E.; Rose, M.; Whittaker, A. R. D. *Aust. J. Chem.* **1994**, *47*, 247−262.

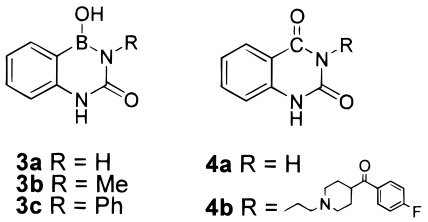
(7) (a) Soloway, A. H.; Zhuo, J.-C.; Rong, F.-G.; Lunato, A. J.; Ives, D. H.; Barth, R. F.; Anisuzzaman, A. K. M.; Barth, C. D.; Barnum, B. A. *J. Organomet. Chem.* **1999**, *581*, 150−155. (b) Lesnikowski, Z. J.; Schinazi, R. F. *Pol. J. Chem.* **1995**, *69*, 827−840. (c) Goudgaon, N. M.; El-Kattan, G. F.; Schinazi, R. F. *Nucleosides Nucleotides* **1994**, *13*, 849−880.

10.1021/jo991176q CCC: $18.00
Published on Web 12/02/1999



1a R = He **2a** R = H
1b R = Me **2b** R = Me

Figure 1.



3a R = H **4a** R = H
3b R = Me **4b** R =
3c R = Ph

Figure 2.

dine nucleus and flanked by two nitrogen atoms.[8] A number of these compounds proved to be too toxic or hydrolytically unstable and therefore were of little use as potential BNCT agents.[7] Recently, several boron-containing nucleosides have been synthesized with a borane, cyanoborane, dihydroxyboryl, or carborane group attached directly to a nucleic acid base.[9] One of our major efforts in developing boron-containing nucleosides has focused on the incorporation of stable boron clusters into various nucleosides. We have synthesized several types of boronated nucleosides with a carborane group tethered to the pyrimidine moiety at the N3- or C5-position.[10] Though a higher percentage of boron in a nucleoside would appear desirable, of greater importance is that these boron analogues simulate more closely the naturally occurring nucleosides in their biochemical attributes. To achieve this objective, we[11] and others[12,13] have attempted to replace the carbonyl function at the 4-position in the pyrimidine nucleus with the B−OH group such as 4-borauracil (**1a**) and 4-borathymine (**1b**) shown in Figure 1. They may be viewed as boron isosteres of naturally occurring pyrimidines, i.e., uracil (**2a**) and thymine (**2b**), respectively. A brief description of the synthesis of benzoborauracils **3a**−**c**, the boron analogue of 2,4-(1*H*,3*H*)-quinazolinediones **4a**,**b** (Figure 2), has been reported by us previously.[11] Subsequently, the synthesis of **3b** and other analogues have also been published elsewhere by Hughes and Smith in 1997.[12] The present paper describes the details of the synthesis, structures, and properties of these benzoborauracils and a ribonucleoside derivative of **3b**.

Results and Discussion

Benzoborauracil. Several benzo-fused boron heterocycles **5**−**8** (Figure 3) are known.[14−16] We first successfully synthesized compound **5b** by reduction of (2-nitrophenyl)boronic acid (**9**) in 50% aqueous acetic acid under platinum oxide catalysis.[15] Recently, this compound was directly prepared by acetylation of (2-aminophenyl)boronic acid (**10**).[14] Compound **5a** was obtained in same way and was converted to the benzo-fused boronated pyrimidine **8a** by treatment with liquid NH_3 followed by its recrystallization from MeOH, elimination of one molecule of methanol, hydrolysis, and lyophilization.[14] The stability of benzo-fused boronated pyrimidines **7** and **8** led to attempts to synthesize 4-borouracil. To investigate the stability of such heterocyclic rings, benzoborauracils **3a**−**c** were first synthesized. Reaction of (2-aminophenyl)boronic acid (**10**) with methyl isocyanate in acetonitrile gave a colorless crystalline solid that was the expected benzoborauracil, 1-hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (**3b**) (Scheme 1). Similarly, addition of phenyl isocyanate to **10** afforded the *N*-Ph-substituted compound **3c**. The N-unsubsituted benzoborauracil **3a** was synthesized by the reaction of **10** with H−N═C═O, generated in situ by the reaction of potassium cyanate with dilute aqueous acetic acid.

The structures of these benzoborauracils **3a**−**c** were established by NMR spectroscopy, mass spectrometry, and microelemental analyses. Compounds **3b** and **3c** were unambiguously confirmed by X-ray crystallographic analyses (see the Supporting Information), which show that the fused benzene ring and heterocyclic ring systems in **3b** and **3c** are essentially coplanar. The dihedral angle between the benzene ring and heterocyclic ring is 2.0(3)° and 3.7(6)° for **3b** and **3c**, respectively. As expected, owing to steric bulk of the phenyl group at N-2 in compound **3c**, the phenyl ring is twisted out of the plane of the heterocyclic ring by 71.4(0.1)°.

The X-ray data show that the structures of heterocyclic system in benzoborauracils is very similar to uracils and benzouracils, as shown by their relative bond lengths (Table 1). The bond lengths of the urea moiety (*d*1, *d*2,

(8) Chissick, S. S.; Dewar, M. J. S.; Maitlis, P. M. *J. Am. Chem. Soc.* **1959**, *81*, 6329−6330.

(9) (a) Graciet, J.-C. G.; Shi, J.; Schinazi, R. *Nucleosides Nucleotides* **1998**, *17*, 711−727. (b) Hasan, A.; Tomasz, J.; Shaw, B. R. *Bioconjugate Chem.* **1997**, *8*, 813−818. (c) Yamamoto, Y.; Imamura, K.-I. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1855−1858. (d) Kattan, G. F.-El; Goudgaon, N. M.; Ilksoy, N.; Huang, J.-T.; Watanabe, K. A.; Sommadossi, J.-P.; Schinazi, R. *J. Med. Chem.* **1994**, *37*, 2583−2588. (e) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734−4736. (f) Schinazi, R. F.; Prusoff, W. H. *J. Org. Chem.* **1985**, *50*, 841. (g) Schinazi, R. F.; Goudgaon, N. M.; Fulcrand, G.; ElKattan, Y.; Lesnikowski, Z.; Ullas, G.; Moravek, J.; Liotta, D. C. *Int. J. Rad. Oncol. Biol. Phys.* **1994**, *28*, 1113−1120.

(10) (a) Rong, F.-G.; Soloway, A. H.; Ikeda, S.; Ives, D. H. *Nucleosides & Nucleotides* **1997**, *16*, 379−401 1997. (b) Lunato, A. J.; Anisuzzaman, A. K. M.; Rong, F.-G.; Ives, D. H.; Ikeda, S.; Soloway, A. H. In *Cancer Neutron Capture Therapy*; Mishima, Y., Ed.; Plenum Press: New York, 1996; pp 151−155. (c) Rong, F. G.; Soloway, A. H.; Ikeda, S.; Ives, D. *Nucleosides & Nucleotides* **1995**, *14*, 1873−1887. (d) Rong, F. G.; Soloway, A. H.; Ikeda, S.; Ives, D. H. *Nucleosides Nucleotides* **1994**, *13*, 2021−2034. (e) Lunato, A. J.; Wang, J.; Woollard, J. E.; Anisuzzaman, A. K. M.; Ji; W.; Rong, F.-G.; Ikeda, S.; Soloway, A. H.; Eriksson, S.; Ives, D. H.; Blue, T. B.; Tjarks, W. *J. Med. Chem.* **1999**, *42*, 3378−3389.

(11) Barnum, B. A.; Beeson, J. C.; Rong, F.-G.; Soloway, A. H.; Tjarks, W.; Jordan IV, G. T.; Shore, S. G. In *Advances in Boron Chemistry*; Siebert, W., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1997; pp 240−243.

(12) Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492−4499.

(13) Matteson, D. S. Unpublished results, personal communication.

(14) Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597−7605.

(15) Soloway, A. H. *J. Am. Chem. Soc.* **1960**, *82*, 2442−2444.

(16) (a) Cai, X. S.; Keana, J. F. W. *Bioconjugate Chem.* **1991**, *2*, 317−322. (b) Vorontsova, L. G.; Chizhov, O. S.; Boldyreva, O. G.; Dorokhov, V. A.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 329−332. (c) Boldyreva, O. G.; Dorokhov, V. A.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 428−430. (d) Zolotarev, B. M.; Dorokhov, V. A.; Lavrinovich, O. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 80−84. (e) Dorokhov, V. A.; Boldyreva, O. G.; Zolotarev, B. M.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 174−180. (f) Dorokhov, V. A.; Zolotarev, B. M.; Boldyreva, O. G.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 411−418. (g) Mikhailov, B. M.; Kuimova, M. E. *J. Organomet. Chem.* **1976**, *116*, 123−133.

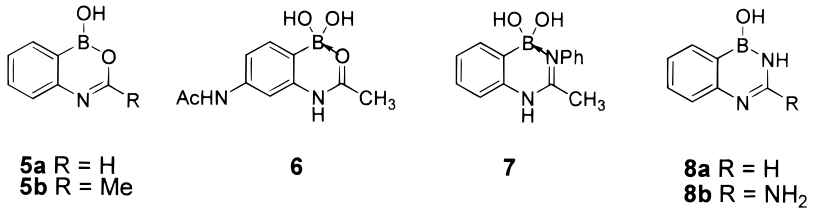


Figure 3.

Scheme 1

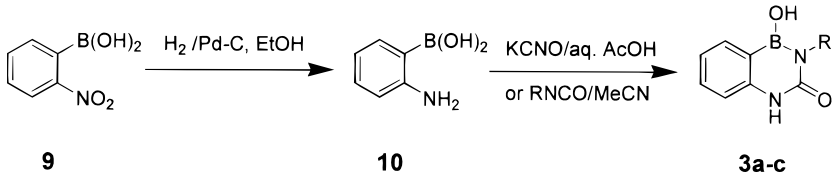
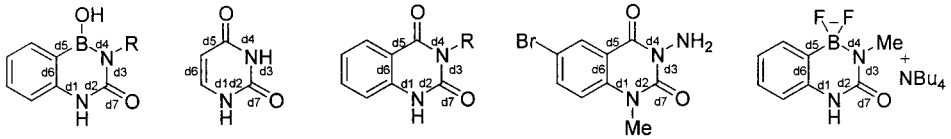


Table 1. Selected Bond Lengths (Å) for Benzoborauracils, Uracils, and Benzouracils



	3a-c	**2a**	**4b**	**11**	**12**		
compd	*d*1	*d*2	*d*3	*d*4	*d*5	*d*6	*d*7
3b	1.389	1.359	1.358	1.451	1.543	1.385	1.241
3c	1.401	1.350	1.373	1.464	1.531	1.393	1.251
2a	1.358	1.371	1.376	1.371	1.430	1.340	1.215
4b	1.400	1.353	1.417	1.408	1.455	1.399	1.225
11	1.387	1.380	1.403	1.371	1.470	1.405	1.214
12	1.401	1.371	1.342	1.517	1.576		1.241

*d*3 and *d*7) in the boracyclic system are comparable to the related bonds in uracil **2a**,[17] benzouracils **4b**,[18] and **11**[19] (Table 1) and are essentially identical to those observed for the tetracoordinated anion **12**.[12] The C−B bond lengths, *d*5 (**3b**: 1.543(4) Å; **3c**: 1.531(3) Å) are slightly shorter than those observed for phenylboronic acid (1.565(3) Å)[20] and tetracoordinated anion **12** (1.576-(6) Å).[12] The B−N bond lengths, *d*4 (**3b**: 1.451(3) Å; **3c**: 1.464(2) Å) are considerably shorter than the B−N single bond (1.57−1.63 Å)[21] as well as those found in tetracoordinated boron compounds (1.517−1.657 Å).[22] They are very close to those observed for borazine (1.44(2) Å),[23] (dimethylamino)dimethylborane (1.42(3) Å),[24] tri(1,3,2-benzodioxaborol-2-yl)amine (1.438(11) Å),[25] and (diphenylmethyleneamino)dimesitylborane (1.38(2) Å).[26] This suggests a partial double bond character of the B−N bond in the benzoborauracils, contributing to the p_z orbital N → B interaction that requires the sp^2 hybridization of the B and N atoms in the heterocycle. The sum of the bond angles around the B and the N atoms in both compounds **3b** and **3c** are exactly 360 °, meeting the requirement of the N → B interaction.

^{11}B NMR is a particularly useful tool for studying the hybridization of the boron atom.[27] The sp^2 hybridization of the B atom can be shown by the ^{11}B shift value. The shift value of ca. 30 ppm (referenced to $Et_2O{\cdot}BF_3$) indicates a trigonal-planar substituted, sp^2-hybridized boron atom, and that of ca. 5 ppm arises from a tetrahedral-substituted, sp^3-hybridized boron atom. The ^{11}B NMR spectra of benzoborauracils **3a**−**c** were recorded in acetone-d_6, DMSO-d_6, and MeOH-d_4.

In acetone-d_6 and DMSO-d_6, a signal at ca. 30 ppm, observed for each compound, is in agreement with the existence of an sp^2-hybridized boron atom in the heterocyclic system. In MeOH-d_4, a new signal at ca. 5 ppm was observed. Accordingly, the NMR shift observed for the benzoborauracils **3a**−**c** is consistent with their transformations from a trigonal planar sp^2-hybridized boron atom to a tetrahedral sp^3-hybridized boron atom; demonstrating the formation of a tetrahedral substituted boron center. This formation in compounds **3a**−**c** in DMSO-d_6/MeOH can be shown in Figure 4 by the ^{11}B NMR spectra.

(17) Stewart, B. F. *Acta Crystallogr.* **1967**, *23*, 1102−1105.
(18) Peeters, O. M.; Blaton, N. M.; De Ranter, C. J. *Cryst. Struct. Commun.* **1982**, *11*, 375−379.
(19) Ardebili, M. H. P.; White, J. G. *Acta Crystallogr.* **1978**, *B34*, 2890−2891.
(20) Rettig, S. J.; Trotter, J. *Can J. Chem.* **1977**, *55*, 3071−3075.
(21) Wells, A. F. *Structural Inorganic Chemistry*; Oxford University Press: London, 1962.
(22) (a) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1977**, *55*, 958−965. (b) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1976**, *54*, 3130−3141. (c) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1975**, *53*, 1393. (d) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1973**, *51*, 1288.
(23) (a) Harshbarger, W.; Lee, G.; Porter, R. F.; Bauer, S. H. *Inorganic Chem.* **1969**, *8*, 1683−1689. (b) Bauer, S. H. *J. Am. Chem. Soc.* **1938**, *60*, 524.
(24) Bullen, G. J.; Clark, N. H. *J. Chem. Soc. A* **1970**, 992−996.
(25) Bullen, G. J.; Maillinson, P. R. *J. Chem. Soc. A* **1970**, 2213−2221.
(26) Bullen, G. J. *J. Chem. Soc., Dalton Trans.* **1973**, 858−863.
(27) (a) Nöth, H.; Wrackmeyer, R. Nuclear magnetic Resonance Spectroscopy of Boron Compounds. In *NMR−Basic Principles and Progress*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; Springer-Verlag: Berlin, 1978. (b) Wrackmeyer, B. *Ann. Rep. NMR Spectrosc.* **1988**, *20*, 61−203. (c) Heřmánek, S. *Chem. Rev.* **1992**, *92*, 325−362.

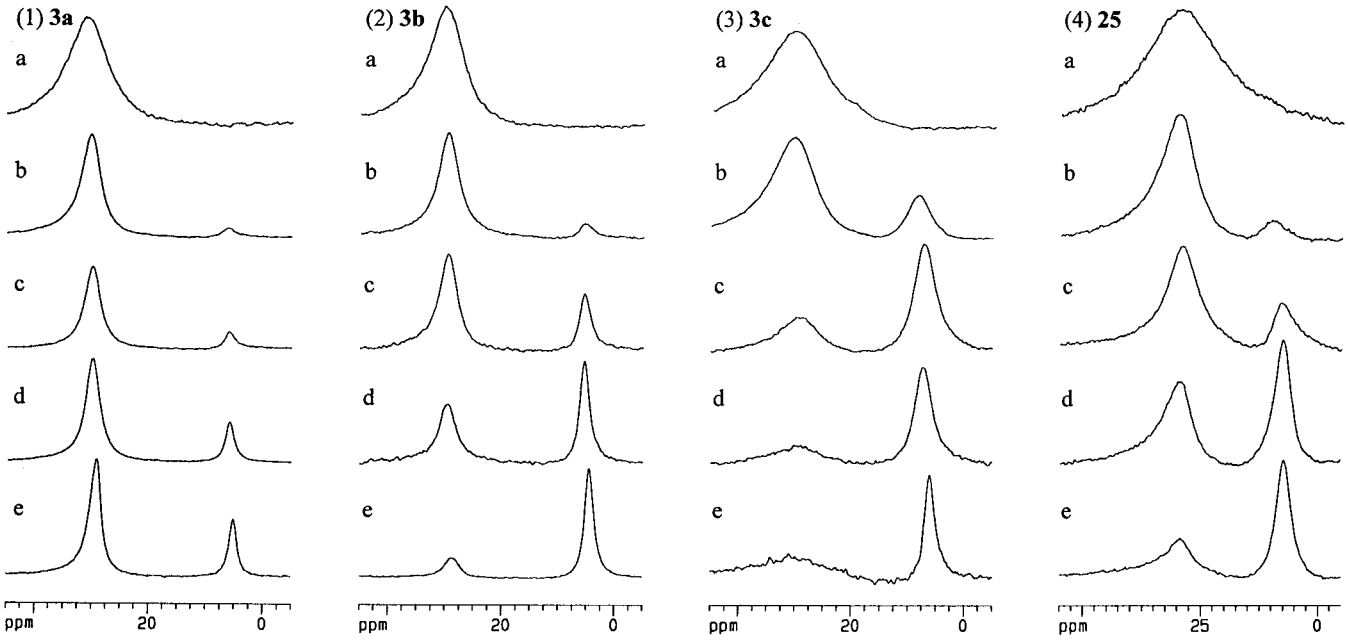


Figure 4. ^{11}B NMR spectra of compounds **3a**−**c** and **25**: (1) **3a** (a) DMSO-d_6; (b) DMSO-d_6/MeOH = 1:1; (c) DMSO-d_6/MeOH = 1:2; (d) DMSO-d_6/MeOH = 1:5; (e) MeOH-d_4; (2) **3b** (a) DMSO-d_6; (b) DMSO-d_6/MeOH = 2:1; (c) DMSO-d_6/MeOH = 1:1; (d) DMSO-d_6/MeOH = 1:2; (e) MeOH-d_4; (3) **3c** (a) DMSO-d_6; (b) DMSO-d_6/MeOH = 5:1; (c) DMSO-d_6/MeOH = 2:1; (d) DMSO-d_6/MeOH = 1:1; (e) MeOH-d_4; (4) **25**, (a) DMSO-d_6; (b) DMSO-d_6/MeOH = 1:1; (c) DMSO-d_6/MeOH = 1:2; (b) DMSO-d_6/MeOH = 1:5; (b) MeOH-d_4.

Table 2. Equilibrium of 3a−c and 13a−c and 25 and 26 in DMSO-d_6/MeOH or MeOH-d_4 As Observed by ^{1}H NMR

DMSO-d_6/ MeOH	**3a**	**13a**	DMSO-d_6/ MeOH	**3b**	**13b**	DMSO-d_6/ MeOH	**3c**	**13c**	DMSO-d_6/ MeOH	**25**	**26**
1:0	100	0	1:0	100	0	1:0	100	0	1:0	100	0
1:1	94	6	2:1	92	8	5:1	75	25	1:1	88	12
1:2	85	15	1:1	70	30	2:1	35	65	1:2	73	27
1:5	80	20	1:2	47	53	1:1	15	85	1:5	42	48
0:1[a]	70	30	0:1[a]	15	85	0:1[a]	∼5	∼95	0:1[a]	22	78

[a] In MeOH-d$_4$.

The equilibrium between a trigonal planar sp^2-hybridized boron atom and a tetrahedral sp^3-hybridized boron atom is dependent upon the solvent systems used and the substituent at N atom. In DMSO-d_6/MeOH, an increased amount of methanol led to the enhancement in the signal at ca. 5 ppm and a diminution of the signal at ca. 30 ppm (Table 2). In DMSO-d_6/MeOH (1:1) solution, phenyl-substituted benzoborauracil **3c** is transformed to its tetrahedral product, which was isolated in 85% yield as a colorless crystalline solid. X-ray crystallographic study of this product revealed it to be a bis-methanol adduct **13c** (see the Supporting Information) of **3c**. In MeOH-d_4 solution, the methyl-substituted benzoborauracil **3b** contains 85% of the bis-methanol adduct **13b**, whereas the unsubstituted analogue **3a** only forms 30% of the adduct **13a**. The equilibrium, as observed by NMR, between **3a**−**c** and **13a**−**c** are summarized in Table 2. From these findings one can infer that the degree of ring strain is a determining factor in the percentage of sp^2- and sp^3-hybridized boron atoms in the compound.

The adduct **13c** is stable in MeOH solution or in the solid state. In DMSO-d_6 solution, **13c** is converted to **3c** by hydrolysis and to **14c** by elimination of 1 equiv of MeOH. In DMSO-d_6/MeOH, both compounds **3c** and **13c** were observed. Increasing the amount of methanol in the mixture shifted the equilibrium to compound **13c**. This indicates the reversible transformation of sp^2-hybridized and sp^3-hybridized boron atoms, which were directly observed in the ^{1}H NMR spectra of compound **13c** in DMSO-d_6/MeOH (see the Supporting Information). A possible mechanism for this reversible transformation is shown in Scheme 2. Groziak et al. observed a similar transformation for 2,4,1-oxaza- and diazaborines that undergo reversible 1,4-additions across the B1 and N4 atoms with water or methanol.[14]

The ready elimination of methanol from the adduct **13c** may be attributed to its weak B−O bond (between the boron atom and the oxygen atom in the urea moiety). The X-ray data of **13c** show that this B−O bond length (1.588(4) Å) is considerably longer than the B−OMe bonds (1.436(4) and 1.448(4) Å) and those observed in tri(1,3,2-benzodioxaborol-2-yl)amine (1.381(5) Å),[25] 2-phenyl-1,3,2-benzodioxaborol (1.394(3) Å),[28] phenylboronic acids (1.371(7) Å).[20] This can be attributed to the O → B interaction in these molecules. The O → B bond observed for (salicyaldehydato)diphenylboron is 1.574(4) Å,[29] slightly shorter than that in **13c**.

The reversible transformation of a sp^2-hybridized and a sp^3-hybridized boron species was also observed for the analogues **3a** and **3b**. In MeOH-d_4 solution, the formation of the corresponding adducts **13a** and **13b** are temperature dependent, with lower temperatures leading to

(28) Zettler, Von F.; Hausen, H. D.; Hess, H. *Acta Crystallogr.* **1974**, *B30*, 1876.
(29) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1976**, *54*, 1168−1175.

Scheme 2

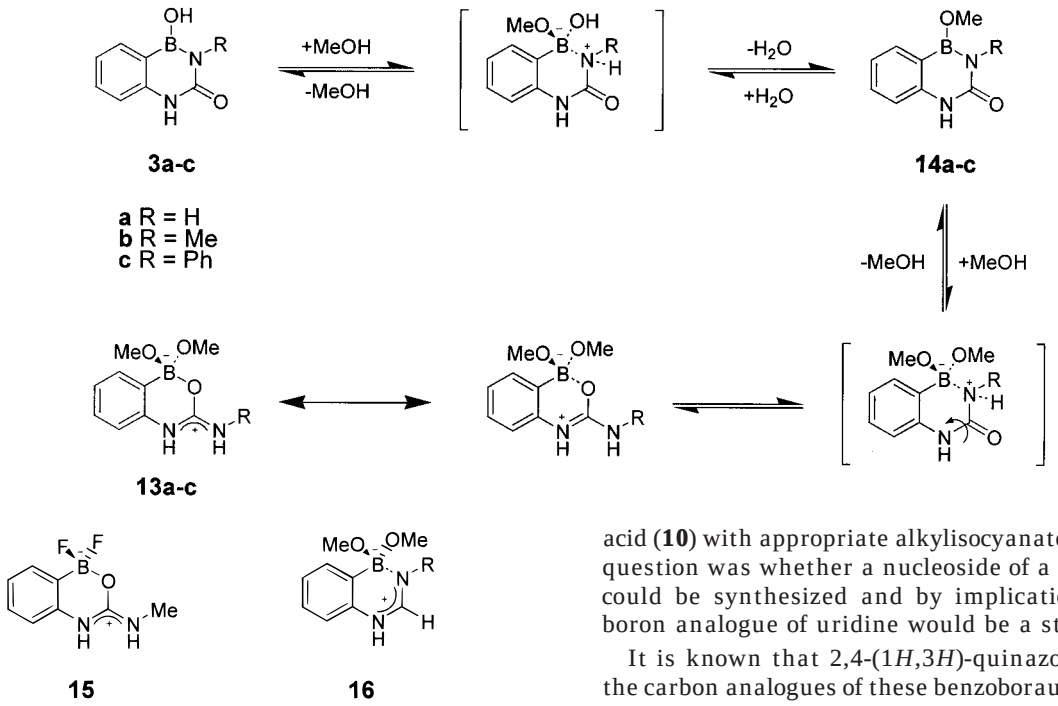


Figure 5.

increased percentages of the **13a** and **13b**. Furthermore, upon removal of methanol, **3a** and **3b** were recovered. This may be due to the longer B−O bond lengths in the adducts **13a** and **13b** as was observed for **13c**. Hughes and Smith[12] also reported a comparable reversible intramolecular rearrangement with the difluoroboronate **15**.

It should be mentioned that the structural data for compound **13c** are very close to those observed for analogue **15**, a proven zwitterion.[12] However, the B−O bond length (1.588(4) Å) is considerably longer than that in compound **15** (1.520(2) Å). Another zwitterion boron heterocycle observed by Groziak et al. is a bis-methanol adduct of 1,2-dihydro-1-hydroxy-2,4,1-benzodiazaborine (**16**) (Figure 5).[14] We observed that the C−N bond lengths in **13c** (1.339(3) Å and 1.331(3) Å) are between those in *N*,*N*,*N*′,*N*′-tetramethylformamidinium perchlorate (1.30-(1) Å)[30] and *N*,*N*,*N*′,*N*′-tetramethylurea (1.3706(13) Å).[31] In addition, the C−O bond length (1.272(3) Å) in **13c** is considerably longer and shorter than that in *N*,*N*,*N*′,*N*′-tetramethylurea (1.226(2) Å) and the C−O single bond (1.43 Å),[32] respectively, but it is between the C═O bond in the O → B interaction (salicyaldehydato)diphenylboron (1.263(4) Å)[29] and in the zwitterion boronate heterocycle **15** (1.285(2) Å). We conclude the possible existence of O → B interaction with the boron atom possessing a limited partial negative charge with the partial positive charge delocalized over the urea moiety in the heterocyclic system.

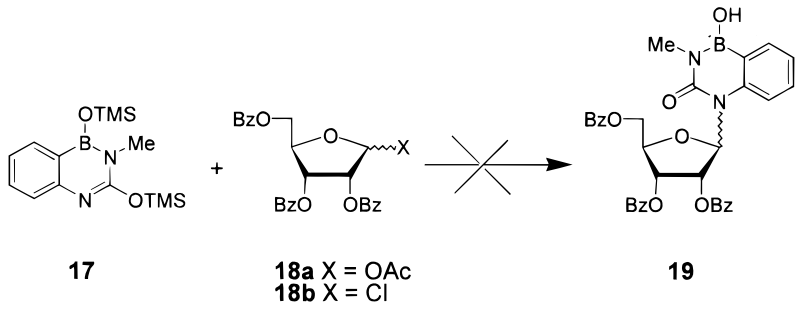
***N*-Methyl Benzoborauracil Nucleoside.** The synthesis of benzoborauracils **3a**−**c** can be conveniently achieved by the condensation of (2-aminophenyl)boronic acid (**10**) with appropriate alkylisocyanates. An important question was whether a nucleoside of a benzoborauracil could be synthesized and by implication whether the boron analogue of uridine would be a stable molecule.

It is known that 2,4-(1*H*,3*H*)-quinazolinediones (**4a**), the carbon analogues of these benzoborauracils **3a**−**c**, can form both ribofuranosyl and deoxyribofuranosyl nucleosides.[33] However, attempts to prepare the benzoborauracil nucleoside were unsuccessful by the procedures for preparing normal nucleosides under various reaction conditions.[34] Condensation of the TMS protected *N*-methyl benzoborauracil **17** and 1-*O*-Ac-2,3,5-tri-*O*-benzoyl-ribofuranose (**18a**) in MeCN with catalytic amounts of trimethylsilyl triflate or $SnCl_4$ resulted in a multiproduct mixture, but it did not afford the desired nucleoside **19** (Scheme 3). Nucleoside formation also did not occur in the reactions of tri-*O*-benzoyl-D-ribofuranosyl chloride (**18b**)[35] with the TMS-protected *N*-methyl benzoborauracil **17** in MeCN with catalytic amounts of trimethylsilyl triflate, CuI, $ZnCl_2$, or $SnCl_4$.

It is known that ribose reacts with aniline to give the corresponding *N*-phenyl sugar.[36] Similarly, condensation of D-ribose and D-deoxyribose **20a**,**b** with **10** gave the corresponding adducts **21a**,**b**, respectively (Scheme 4). Unfortunately, reaction of **21a**,**b** with methylisocyanate in MeCN or DMSO did not give the expected nucleosides **22a**,**b**, respectively. This may be due to the free hydroxyl groups on the carbohydrate moiety. Thus, the hydroxyl groups in D-ribose **20b** were protected first by condensation with acetone under acidic conditions followed by treatment with TBDMSCl producing compound **23**.[37] Reaction of the latter compound with **10** followed by condensation with methylisocyanate afford the desired nucleoside **25**. The ^{1}H NMR spectrum indicates that crude product **25** consists of anomeric isomers in approximately 2:1 ratio. After chromatography, only the major product was obtained in 82% yield, indicating that the minor product undergoes subsequent anomerization

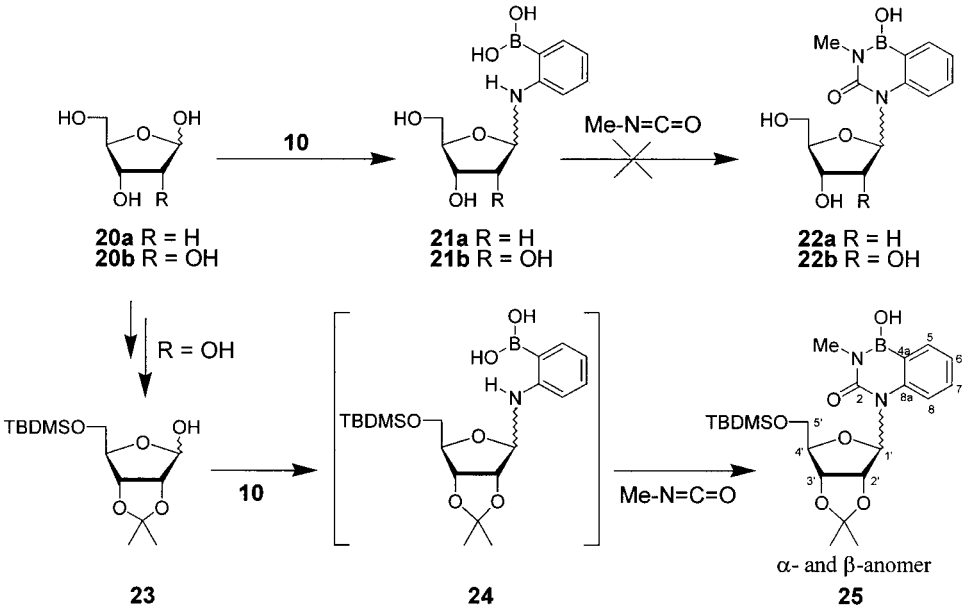
(30) Prick, P. A. J.; Beurskens, P. T. *Cryst. Struct. Commun*. **1979**, *8*, 293−298.
(31) Frampton, C. S.; Parkes, K. E. B. *Acta Crystallogr*. **1996**, *C52*, 3246−3248.
(32) Allen, F. A.; Kennard, O.; Waston, D. G.; Brammer, L.; Orpen, A. G.; Tayler, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.
(33) Stout, M. G.; Robins, R. *J. Org. Chem*. **1968**, *33*, 1219−1225.
(34) Townsend, L. B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, NY, 1988.
(35) Kissman, H. M.; Pidacks, D.; Baker, B. R. *J. Am. Chem. Soc.* **1955**, *77*, 18−24.
(36) Chavis, C.; De Gourcy, C.; Dumont, F.; Imbach, J.-L. *Carbohydr. Res*. **1983**, *113*, 1−20.
(37) Kaskar, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031−1032.

Scheme 3



17 **18a** X = OAc **18b** X = Cl **19**

Scheme 4



20a R = H **20b** R = OH **21a** R = H **21b** R = OH **22a** R = H **22b** R = OH **23** **24** **25**

during chromatography on silica gel. The major product also undergoes anomerization in $CDCl_3$ solution with the minor product (~5%) being observed after a few days.

To determine whether the structure of **25** is the α- or *β*-anomer, 2D $^1H-^1H$ NOESY experiments were carried out in $CDCl_3$ solution. The assignments of the chemical shifts of the protons at the sugar moiety were achieved on the basis of 2D $^1H-^1H$ COSY experiments. The 2D $^1H-^1H$ NOESY spectrum indicates that the C(1′)−H proton at $\delta = 6.79$ (d, $J = 4.7$ Hz) shows an enhanced NOE with C(2′)-H ($\delta = 5.09$ ppm, dd, $J = 6.6$, 4.7 Hz), C(3′)-H (4.99 (dd, $J = 6.6$, 0.6 Hz), and C(5′)-H ($\delta = 3.83$ ppm, dd, $J = 15.0$, 3.3 Hz and $\delta = 3.79$ ppm, dd, $J = 15.0$, 2.9 Hz). In addition, an enhanced NOE was also observed between C(8)-H ($\delta = 7.92$ ppm, dd, $J = 8.8$, 1.0 Hz) and C(4′)-H ($\delta = 4.41$ ppm, dd, $J = 2.6$, 2.3 Hz). MM+ calculations indicate a distance between the C(8)-H and C(4′)-H protons of 3.04 Å in the α-anomeric configuration and 4.16 Å in the *β*-anomeric configuration.[38] Thus, the NOESY results are in good agreement with the α-anomeric configuration for compound **25**, the predominant structure in $CDCl_3$.

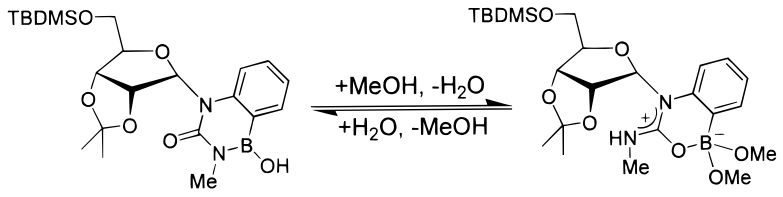
The ^{11}B signal of the nucleoside **25** was observed at 29.5 ppm in DMSO-d_6 solution. The addition of methanol generated a new signal at ca. 7 ppm [see (4) in Figure 4], indicating a tetrahedral substitued sp^3-hybridized boron center. As observed for benzoborauracils **3a**−**c**, the signal at ca. 7 ppm was enhanced with increasing amounts of methanol (Table 2). About 78% of compound **25** was transformed to the corresponding bis-methanol adduct **26** in MeOH-d_4 solution, a slightly lower percentage than that observed for **3b**. Compound **25** could be recovered after evaporation of methanol, demonstrating that the transformation between the sp^3-hybridized boron center and the sp^2-hybridized boron center is reversible (Scheme 5).

Conclusions

This work shows that the benzoborauracils and a derived ribose nucleoside can be conveniently synthesized and are chemically stable. Bis-methanol adducts **13a**−**c** and **26**, rearrangement products of **3a**−**c** and **25**, respectively, could only be observed in the presence of methanol. Upon solvent evaporation, the benzoborauracils and the nucleoside were recovered. However, **13c**, a colorless crystalline solid, was isolated in 85% yield from the methanolic solution of **3c**. In the case of compounds **3b**,**c**, the comparable adduct **13b**,**c** could not be obtained. This suggests the heterocyclic ring structure [−C═CB(OH)-NC(O)N−] is generally stable. It remains to be determined whether the boron analogues of the naturally occurring bases, such as 4-borauracil and 4-borathymine, can be prepared and if these structures are actually as resistant toward hydrolytic/physiological conditions, decomposition and rearrangement as are their corresponding benzo analogues. Standard glycosylation procedures on a benzoborauracil base failed to produce the required

(38) HyperChem Release 5.1, Hypercube, Inc., 1997.

Scheme 5



25 **26**

benzoborauracil nucleoside. The alternative route, as shown in Scheme 4, resulted in the formation of the nucleoside in an α-anomeric configuration according to NOE-NMR data. The synthesis of 4-borauridine/4-borathymidine with the biologically relevant *β*-configuration remains to be accomplished.

Experimental Section

General Procedures and Materials. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Coupling constants (*J*) are reported in hertz. ^{11}B chemical shifts were referenced to external $BF_3{\cdot}OEt_2$ (δ = 0.0 ppm) with a negative sign indicating an upfield shift. Flash column chromatography was carried out on Merck silica gel 60 (0.040−0.063 mm, 230−400 Mesh). The reagents were purchased from various chemical companies and used directly without further purification unless otherwise specified. Anhydrous ethyl ether and tetrahydrofuran (THF) were distilled from sodium/diphenyl ketone. Benzene and acetonitrile were distilled from CaH_2. Chloroform ($CHCl_3$) and carbon tetrachloride (CCl_4) were distilled from P_2O_5. 2-Nitrophenylboronic acid and 2-aminophenylboronic acid were prepared according to literature procedures.[12] Phenylboronic acid, potassium isocyanate, methyl isocyanate, phenyl isocyanate, and HMDS were purchased from the Aldrich Chemical Co. Palladium (10%) on charcoal was purchased from either Aldrich Chemical Co or Strem Chemical Co. Acetic anyhdride, acetic acid, fuming nitric acid, methanol, and absolute ethanol were used as received from Fisher Scientific. Acetonitrile and tetrahydrofuran and were purchased from Fisher and purified before use.

1-Hydroxy-1*H*-2,4,1-benzodiazaborin-3-one (3a). Potassium isocyanate (182 mg, 2.24 mmol) was added to a stirred solution of **10** (288 mg, 2.104 mmol) in glacial acetic acid (5 mL) and water (30 mL). After the mixture was stirred for 2 min at room temperature, a white precipitate began to form, and the reaction was continued for 14 h after which time it was cooled at 0 °C for 1 h. The mixture was filtered, washed with water, and dried in vacuo to give 248 mg (73%) of **3a** as pale fine yellow needles: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 10.00 (br s, 1H, N(1)-*H*), 8.65 (s, 1H, BO*H*), 7.90 (br, 1H, N(3)-*H*), 7.83 (dd, *J* = 7.3, 1.4, 1H, C(5)-*H*), 7.39 (ddd, *J* = 8.2, 7.3, 1.4, 1H, C(7)−H), 7.00 (d, *J* = 8.2, 1H, C(8)-*H*), 6.96 (t, *J* = 7.3, 1H, C(6)−H); ^{13}C NMR (DMSO-d_6) δ 154.6 (C═O), 146.6 (C(8a)), 132.3, 132.1, 120.5, 114.6 (br, C(4a)), 114.3; ^{11}B NMR (DMSO-d_6) δ 31.1; ^{11}B NMR (MeOH-d_4) δ 29.3; ^{11}B NMR (acetone-d_6) δ 30.9; IR (KBr) 3233vs (br), 1684vs; HRMS calcd for $C_7H_7BN_2O_2$ 162.0601, found 162.0604. Anal. Calcd for $C_7H_7BN_2O_2{\cdot}H_2O$: C, 46.72; H, 5.04; N, 15.57; B, 6.01. Found: C, 46.46; H, 4.67; N, 15.11; B, 6.44.

1-Hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (3b). Methyl isocyanate (0.2 mL, 3.30 mmol) was added via a syringe to a stirred solution of **10** (261 mg, 1.904 mmol) dissolved with gentle heating in acetonitrile (15 mL). After the mixture was stirred for 2 min at room temperature, a white solid began to form, and the reaction was continued for 4 h. The mixture was filtered, washed with hot acetonitrile, and dried in vacuo to give 291.5 mg (87%) of **3b** as a colorless crystalline solid: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 10.27 (br s, 1H, N(1)-*H*), 9.18 (s, 1H, BO*H*), 7.93 (1H, dd, *J* = 7.3, 1.0, C(5)-*H*), 7.40 (1H, ddd, *J* = 8.2, 7.3, 1.0, C(7)-*H*), 7.01 (1H, dd, *J* = 8.2, 0.6, C(8)-*H*), 6.98 (1H, td, *J* = 7.3, 0.6, C(6)-*H*), 2.98 (3H, s, CH_3); ^{13}C (DMSO-d_6) δ 155.1 (C═O), 145.4 (CN), 132.3, 132.2, 120.4, 114.0, 113.8 (br, CB), 27.3 (CH_3); ^{11}B NMR (DMSO-d_6) δ 30.3; ^{11}B NMR(MeOH-d_4) 28.7; ^{11}B NMR (acetone-d_6) 30.7; IR (KBr) 3354vs, 1641vs, 1563vs; HRMS calcd for $C_8H_9BN_2O_2$ 176.0757, found 176.0767. Anal. Calcd for $C_8H_9BN_2O_2$: C, 54.60; H, 5.15; N, 15.92; B, 6.14. Found: C, 54.50; H, 5.13; N, 15.78; B, 6.26.

1-Hydroxy-2-phenyl-1*H*-2,4,1-benzodiazaborin-3-one (3c). Phenyl isocyanate (20 *μ*L, 0.184 mmol) was added via a syringe to a stirred solution of **10** (39.3 mg, 0.287 mmol) in acetonitrile (3 mL). After being stirred for 18 h at room temperature, the mixture was filtered and dried in vacuo. The product was recrystallized from ethyl acetate to give 48.7 mg (73%) of **3c** as colorless needles: mp 197.5−198.5 °C; ^{1}H NMR (DMSO-d_6) δ 10.40 (br s, 1H, N(1)-*H*), 9.04 (s, 1H, BO*H*), 7.99 (1H, d, *J* = 7.4, C(5)-*H*), 7.46 (1H, ddd, *J* = 8.0, 7.4, 1.0, C(7)−H), 7.38 (m, 2H, Ph-*H*), 7.28 (m, 1H, Ph-*H*), 7.15 (m, 2H, Ph-*H*), 7.08 (1H, d, *J* = 8.0, C(8)-*H*), 7.03 (1H, t, *J* = 7.4, C(6)-*H*); ^{13}C (DMSO-d_6) δ 153.9, 145.4, 139.0, 132.4, 132.3, 128.6 (2C), 128.0 (2C), 125.9, 120.4, 114.0 (The resonance assigned to C−B was unobservable due to strong quadurupolar line-broadening); ^{11}B NMR (DMSO-d_6) δ 30.5; ^{11}B NMR (MeOH-d$_4$) δ 30.5; ^{11}B NMR (acetone-d_6) δ 30.0; IR (KBr) 3292s, 1634vs, 1564vs; HRMS calcd for $C_{13}H_{11}BN_2O_2$ 238.0914, found 238.0921. Anal. Calcd for $C_{13}H_{11}BN_2O_2$: C, 65.59; H, 4.66; N, 11.77; B, 4.54. Found: C, 64.86; H, 4.61; N, 11.51; B, 4.73.

Bis-methanol Adduct of 1-Hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (13a). A sample of **3a** (20 mg) was dissolved in methanol-d_4. ^{1}H NMR spectrum analysis showed that the solution contained **13a** (30%) and **3a** (70%): ^{1}H NMR (MeOH-d_4) δ 7.37 (1H, dd, *J* = 7.3, 1.3, Ar), 7.17 (1H, dd, *J* = 8.0, 7.3, 1.3, Ar), 7.03 (1H, m, Ar), 6.78 (1H, d, *J* = 8.0, Ar); ^{13}C NMR (MeOH-d_4) δ 160.0 (C═O), 140.3 (C−N), 132.8 (CH), 128.7 (CH), 124.8 (CH), 115.0 (CH); ^{11}B NMR (MeOH-d_4) δ 5.1.

Bis-methanol Adduct of 1-Hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (13b). A sample of **3b** (15 mg) was dissolved in methanol-d_4. ^{1}H NMR spectrum analysis showed that the solution contained **13b** (85%) and **3b** (15%): ^{1}H NMR (MeOH-d_4) δ 7.37 (1H, dd, *J* = 7.2, 1.0, Ar), 7.17 (1H, dd, *J* = 8.0, 7.2, 1.0, Ar), 7.04 (2H, m, Ar); ^{13}C NMR (MeOH-d$_4$) δ 159.0 (C═O), 140.6 (C−N), 132.8 (CH), 128.8 (CH), 124.6 (CH), 114.9 (CH), 27.2 (Me); ^{11}B NMR (MeOH-d_4) δ 4.5.

Bis-methanol Adduct of 1-Hydroxy-2-phenyl-1*H*-2,4,1-benzodiazaborin-3-one (13c). Methanol (15 mL) was added to a solution of compound **3c** (120 mg, 0.5 mmol) in dimethyl sulfoxide (DMSO, 3 mL) at room temperature. The precipitate formed was filtered, washed with methanol, and dried to give 120 mg (85%) of **13c** as a colorless crystalline solid: mp 168−169 °C; ^{1}H NMR (MeOH-d_4) δ 9.86 (1H, br, NH), 9.37 (1H, br, NH), 7.41 (2H, m, Ph), 7.35 (3H, m, Ph), 7.17 (2H, m, Ph), 7.05 (1H, td, *J* = 7.3, 0.8, Ar), 6.85 (1H, d, *J* = 8.0, Ar), 3.35 (6H, s, 2 OMe); ^{1}H NMR (DMSO-d_6/MeOH = 1:1) δ 10.04 (1H, br, NH), 9.54 (1H, br, NH), 7.37 (2H, m, Ph), 7.32 (2H, m, Ph), 7.26 (1H, dd, *J* = 7.2, 1.0, Ar), 7.14 (1H, dd, *J* = 8.0, 7.2, 1.0, Ar), 7.11 (1H, m, Ph), 7.00 (1H, t, *J* = 7.2, Ar), 6.83 (1H, d, *J* = 8.0, Ar), 3.24 (6H, s, 2 OMe); ^{13}C NMR (MeOH-d$_4$) δ 157.1 (C═O), 140.1 (C), 137.5 (C), 132.6 (CH), 130.3 (2 CH), 129.0 (CH), 126.5 (CH), 125.2 (CH), 123.1 (2 CH), 115.7 (CH), 50.0 (MeO).^{13}C NMR (DMSO-d_6/MeOH = 1:1) δ 156.3 (C═O), 139.7 (C), 137.4 (C), 132.3 (CH), 129.8 (2 CH), 128.2 (CH), 125.4

(CH), 124.4 (CH), 122.0 (2 CH), 115.4 (CH), 49.8 (MeO); ^{11}B NMR (MeOH-d_4) δ 6.1; ^{11}B NMR (DMSO-d_6/MeOH = 1:1) δ 7.3; IR (KBr) 3369−2650br, 1633s, 1587s, 1556s; HRMS calcd for $C_{15}H_{18}BN_2O_3$ (M + H) 285.1410, found 285.1395, and for $C_{14}H_{13}BN_2O_2$ (M − MeOH) 252.1070, found 252.1079.

1-Methoxy-2-phenyl-1*H*-2,4,1-benzodiazaborin-3-one (14c). ^{1}H NMR spectrum of compound **13c** (10 mg) in DMSO-d_6 (0.5 mL) indicated that the solution contains a mixture of **14c** (75%), **13c** (7%), and **3c** (18%): ^{1}H NMR (DMSO-d_6) δ 10.51 (br s, 1H, N*H*), 7.99 (1H, d, J = 7.4, C(5)-*H*), 7.50 (1H, ddd, J = 8.0, 7.4, 1.0, C(7)−H), 7.38 (m, 2H, Ph-*H*), 7.29 (m, 1H, Ph-*H*), 7.16 (m, 2H), 7.13 (1H, d, J = 8.0, C(8)-*H*), 7.06 (1H, t, J = 7.4, C(6)-*H*), 3.74 (s, 3H, MeO); ^{13}C (DMSO-d_6) δ 153.9, 145.6, 139.5, 132.6 (2 C), 129.0 (2C), 128.4 (2C), 126.5, 120.9, 114.7, 113.8 (C−B), 54.6 (OMe); ^{11}B NMR (DMSO-d_6) δ 29.3.

[2-[*N*-(Deoxy-D-ribofuranosyl)amino]phenyl]boronic Acid (21a). 10 (70 mg, 0.51 mmol) was added to a solution of 2-deoxy-D-ribose (75 mg, 0.5 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced presure. The residue was treated with ether, filtered, and dried in vacuo to afford 260 mg of **21a** (97%): ^{1}H NMR(DMSO-d_6) δ 7.46 (dd, J = 7.4, 1.7, 1H, Ar-*H*), 7.24 (ddd, J = 8.3, 7.4, 1.7, 1H, Ar-*H*), 6.74 (d, J = 8.3, 1H, Ar-*H*), 6.59 (td, J = 7.4, 0.4, 1H,Ar-*H*), 6.47 (d, J = 8.0, 1H, NH), 5.36 (m, 1H, C(1′)-H), 4.94 (ddd, J = 7.7, 3.0, 2.8, 1H, C(4′)-H), 4.59 (dt, J = 7.7, 3.0, 2.8, 1H, C(3′)-H), 3.69 (dd, J = 13.0, 3.0, 1H, C(5′)-H), 3.49 (dd, J = 13.0, 2.8, 1H, C(5′)-H), 2.44 (ddd, J = 16.0, 7.1, 2.8, C(2′)-H), 2.12 (dd, J = 16.0, 3.0, C(2′)-H); ^{13}C NMR(DMSO-d_6) δ 151.5 (C(2)), 136.4, 133.1, 116.7 and 111.0 (4 CH), 109.8 (C, C−B), 76.0 (C(2′)), 73.9, 72.4, 62.7, 29.9 (C(3′); IR (KBr) 3424s, 3410s, 1602vs, 1575vs; HRMS calcd for $C_{11}H_{16}BNO_5$ 253.1121, found 253.1097.

[2-[*N*-(D-ribofuranosyl)amino]phenyl]boronic Acid (21b). This compound was prepared from **20b** using the method for **21a** (97%): ^{1}H NMR(DMSO-d_6) δ 7.51 (dd, J = 7.4, 1.5, 1H, Ar-*H*), 7.23 (ddd, J = 8.2, 7.4, 1.5, 1H, Ar-*H*), 7.02 (d, J = 10.3, 1H, NH), 6.83 (d, J = 8.2, 1H, Ar-*H*), 6.64 (t, J = 7.4, 1H, Ar-*H*), 5.7 (d, J = 2.5, 1H, B−OH), 5.22 (d, J = 10.3, 1H, C(1′)-H), 4.25 (br s, 1H), 4.10 (br s, 1H), 4.00 (br s, 1H), 3.65 (s, 2H, C(5′)-H$_2$);^{13}C NMR (DMSO-d_6) δ 150.4 (C(2)), 135.5, 131.5, 117.0, 111.9, 79.7, 72.9, 69.1, 66.3, 64.6; IR (KBr) 3393vs, 1602vs, 1576vs; HRMS calcd for $C_{11}H_{16}BNO_6$ 269.1071, found 269.1103.

4-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl]-1-hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (25). 10 (135 mg, 1 mmol) was added to a solution of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranose (**23**, 305 mg, 1 mmol) in EtOH (10 mL). The mixture was stirred at room temperature for 3 d. The solvent was evaporated under reduced pressure. The residue was dissolved in benzene (10 mL), and methyl isocyanate (0.07 mL, 1 mmol) was added to the solution. The resulting mixture was allowed to stand at room temperature for 1 d. After evaporation of the solvent, the residue was flash chromatographed (EtOAc/hexane = 1:4) to afford 380 mg of **25** (82%) as a colorless crystalline solid: mp 126.3−127.3 °C; ^{1}H NMR-($CDCl_3$) δ 7.92 (dd, J = 8.8, 1.0, 1H, C(8)−H), 7.58 (dd, J = 7.5, 1.7, 1H, C(5)−H), 7.45 (ddd, J = 8.8, 7.0, 1.7, 1H, C(7)−H), 7.08 (ddd, J = 7.5, 7.0, 1.0, 1H, C(6)−H), 6.79 (d, J = 4.7, 1H, C(1′)-H), 5.09 (dd, J = 6.6, 4.7, 1H, C(2′)-H), 4.99 (dd, J = 6.6, 0.6, 1H, C(3′)-H), 4.49 (ddd, J = 3.3, 2.9, 0.6, 1H, C(4′)-H), 3.83 (dd, J = 15.0, 3.3, 1H, C(5′)-H), 3.79 (dd, J = 15.0, 2.9, 1H, C(5′)-H), 3.17 (s, 3H, N-Me), 1.46 and 1.35 (2 s, 2 × 3H, CMe_2), 0.95 (s, 9H, CMe_3), 0.11 and 0.10 (2 s, 2 × 3H, $SiMe_2$); ^{13}C NMR($CDCl_3$) δ 155.9 (C(2)), 145.1 (C(4a)), 131.5 (CH, Ar), 129.7 (CH, Ar), 121.5 (CH, Ar), 119.7 (CH, Ar), 113.2 (C, −OCO-), 90.6 (C(1′)), 82.2, 82.0, 80.7, 65.2 (C(5′), 28.6 (NMe), 25.9 ($SiCMe_3$), 25.2 (Me), 23.4 (Me), 18.2 ($SiCMe_3$), −5.4 and −5.7 ($SiMe_2$); ^{11}B NMR($CDCl_3$) δ 29.7; ^{11}B NMR(DMSO-d_6) δ 29.5; ^{11}B NMR (MeOH-d$_4$) δ 29.3; IR (KBr) cm^{-1} 3354 br, 1618vs, 1594vs; HRMS calcd for $C_{22}H_{35}BN_2O_6Si$ 462.2357, found 462.2350. Anal. Calcd for $C_{22}H_{35}BN_2O_6Si$: C, 57.14; H, 7.63; N, 6.06; B, 2.34. Found: C, 57.23; H, 7.77; N, 5.89; B, 2.02.

Bis-methanol Adduct of 4-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-α-D-ribofuranosyl]-1-hydroxy-2-methyl-1*H*-2,4,1-benzodiazaborin-3-one (26). A sample of **25** (15 mg) was dissolved in methanol-d_4. ^{1}H NMR spectrum analysis showed that the solution contained **26** (78%) and **25** (22%): ^{1}H NMR (MeOH-d_4) δ 7.42 (1H, dd, J = 7.2, 1.6, Ar), 7.24 (1H, ddd, J = 8.0, 7.2, 1.6, Ar), 7.14 (1H, td, J = 7.2, 0.8, Ar), 7.03 (1H, d br, J = 8.0, Ar), 6.16 (1H, d, J = 3.8, C(1′)-H), 4.94 (1H, dd, J = 6.3, 3.8, C(2′)-H), 4.92 (1H, d, J = 6.3, C(3′)-H), 4.41 (1H, dd, J = 2.6, 2.3, C(4′)-H), 3.91 (1H, dd, J = 11.0, 2.6, C(5′)-H), 3.86 (1H, dd, J = 11.0, 2.3, C(5′)-H), 2.95 (s, 3H, N-Me), 1.44 and 1.35 (2 s, 2 × 3H, CMe_2), 0.91 (s, 9H, CMe_3), 0.13 and 0.11 (2 s, 2 × 3H, $SiMe_2$); ^{13}C NMR (MeOH-d_4) δ 160.6 (C═O), 143.9 (Ar, CN), 133.1 (CH, Ar), 128.9 (CH, Ar), 125.7 (CH, Ar), 122.6 (CH, Ar), 118.5 (br, CB), 114.2 (C, OCO), 93.5 (C(1′)), 83.8, 83.1, 81.5, 66.8 (C(5′), 49.8 (2 MeO), 28.1 (NMe), 25.4 ($SiCMe_3$), 25.8 (Me), 23.7 (Me), 19.0 ($SiCMe_3$), −5.5 and −5.6 ($SiMe_2$); ^{11}B NMR (MeOH-d_4) δ 7.3.

Attempt To Synthesize the Nucleoside 19 by Condensation of 17 with 18a,b. The Hilbert−Johnson silyl reaction was employed to synthesize the boron-containing nucleosides. Compound **3b** was dissolved in dry THF. Hexamethyldisilazane (HMDS) (2 equiv) and catalytic amounts of TMSCl (0.01 equiv) were added, and the solution was refluxed. The byproduct, NH_4Cl, sublimed and was periodically removed from the condensor tip when necessary. The cessation of NH_4Cl sublimation indicated the completion of reaction. Removal of THF and excess HMDS by evaporation left clear oily residues that were TMS-protected benzoborauracil **17** and were used immediately for the condensation. The oils were dissolved in MeCN or $CHCl_3$ and freshly prepared 2,3,5-tri-*O*-benzoylribofuranosyl chloride (1.25 equiv), and appropriate catalysts (CuI, or $ZnCl_2$ or $SnCl_4$ or $TMSSO_3CF_3$, 0.01 equiv) were added. The reactions were stirred for up to 2 d. TLC (4:1 hexanes−ethyl acetate) showed a multiproduct mixture. After flash chromatography, no expected nucleoside **19** was obtained and the starting materials **3b** and **18b** were not recovered. About 30% of 2,3,5-tri-*O*-benzoylribofuranose, a hydrolysis product of **18b**, was obtained in the reaction. Similarly, the reactions of the TMS-protected benzoborauracil **17** with α-D-2-deoxy-3,5-di-*O*-*p*-toluoylribofuranosyl chloride and $ZnCl_2$ (0.01 equiv) in CCl_4 or $CHCl_3$ or with 1-*O*-Ac-2,3,5-tri-*O*-benzoylribofuranose and $SnCl_4$ or $TMSSO_3CF_3$ in MeCN did not produce the expected nucleoside.

Structure Determination for 3b,c and 13c. Single crystals of **3b** were grown by recrystallization from acetone, **3c** from ethyl acetate and **13c** from methanol solution. Crystals of suitable size were mounted in glass capillaries and sealed under nitrogen. The crystallographic data were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Unit cell parameters were obtained by a least-squares refinement of the angular setting from 25 reflections, well distributed in reciprocal space and lying in a 2θ range of 24−30°. All reflection data were corrected for Lorentz and polarization effects.

The structures of compounds **3b** and **3c** were solved by the direct methods Multan 11/82 and difference Fourier synthesis with analytical atomic scattering factors used throughout the structure refinement with both the real and imaging components of the anomalous dispersion included for all non-hydrogen atoms using MOLEN[39] on a Dec Vax Station 3100 computer. The molecular structure of **13c** was solved by SHELXTL[40] on a PC. Full-matrix least-squares refinements were employed. After all of the non-hydrogen atoms were located and refined, hydrogen atoms were located from the difference map. All hydrogen atoms were refined isotropically, and all non-hydrogen atoms were refined anisotropically.

Acknowledgment. This work was supported by U.S. Department of Energy Grants (DE-FG02-90ER60972 and DE-AC02-76CH000616) and NCI R01

(39) MOLEN Crystal Structure Analysis, Enraf-Nonius, 1990.
(40) SHELXTL (Version 5.1), Bruker Analytic X-ray Systems, 1997

CA-53896 and the Ohio State University Comprehensive Cancer Center Grant (P30 CA-16058). The X-ray work was supported by NSF Grant CHE91-04035 and a Proctor and Gamble Graduate Fellowship to G.T.J. This investigation was supported by the National Cancer Institute, National Research Service Award (NRSA) CA-09338, Division of Cancer Prevention and Control, to B.A.B. We wish to acknowledge the support of the Ohio State University Campus Chemical Instrument Center.

Supporting Information Available: ^{1}H NMR (400 MHz) spectra of compounds **3a**−**c**, **13c,** and **25** in DMSO-d_6/MeOH, 2D ^{1}H−^{1}H COSY, NOESY, and ROESY spectra of compound **25**, table of the reaction of **17** and **18a**,**b** under various conditions, ORTEP drawings, atomic coordinates, bond lengths and angles, thermal parameters, and least-squares planes for **3b**,**c** and **13c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991176Q